Sclerotherapy with OK-432 for the treatment of symptomatic lymphocele after lymph node dissection

Uyulmaz, Semra ; Puippe, Gilbert ; Büyükakyüz, Nilgün ; Giovanoli, Pietro ; Pfammatter, Thomas ; Lindenblatt, Nicole

Abstract: OBJECTIVE: This study aimed to determine the benefits of sclerotherapy with OK-432 for the treatment of postoperative chronic lymphocele. BACKGROUND: Postoperative chronic lymphocele formation is common and accounts for a high postoperative morbidity. Nonsurgical strategies comprise repetitive percutaneous fluid aspiration or percutaneous sclerotherapy. OK-432 has been used to treat congenital lymphatic malformations with several reports of promising results. We hypothesized that it is more beneficial than repetitive percutaneous fluid aspiration for the treatment of symptomatic lymphocele. METHODS: Two cohorts of melanoma patients who developed recurrent lymphocele after lymph node dissection from January 2013 to August 2017 were compared. The first cohort was treated with repetitive percutaneous fluid aspiration (n = 20). The second cohort received OK-432 sclerotherapy (n = 20). Primary end points were overall treatment duration, number of treatment sessions, and the clinical success in both cohorts. Secondary end points were surgical site infection rate, need for additional antibiotic treatment, wound healing disorders, and the need for revision surgery. RESULTS: Mean overall duration of treatment with sclerotherapy was significantly shorter than with repetitive aspiration (9.4 ± 7.2 vs 47.5 ± 31.9 days, $P < 0.01$). Mean number of sclerotherapy treatment sessions were 2.5 ± 1.2. Clinical success with OK-432 was 19 of 20, and that with repeated aspiration was 7 of 20 (= 15.82, $P < 0.001$). No surgical site infection occurred in the sclerotherapy cohort, which was significantly lower than those treated with repetitive aspiration ($P < 0.03$). Surgical revision was mandatory in 12 of 20 patients who were treated with repetitive aspiration, and only 1 of 20 patients in the sclerotherapy cohort. CONCLUSION: Sclerotherapy with OK-432 for the treatment of postoperative lymphocele is highly beneficial with a significant reduction of morbidity and the overall treatment time compared with repetitive aspiration.

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Sclerotherapy With OK-432 for the Treatment of Symptomatic Lymphocele After Lymph Node Dissection

A Retrospective Comparative Cohort Study

Semra Uyulmaz, MD,[a] Gilbert Puippe, MD,[b] Nilgün Büyükakyüz, MD,[a] Pietro Giovanoli, MD,[a] Thomas Pfammatter, MD,[b] and Nicole Lindenblatt, MD[a]

Objective: This study aimed to determine the benefits of sclerotherapy with OK-432 for the treatment of postoperative chronic lymphocele.

Background: Postoperative chronic lymphocele formation is common and accounts for a high postoperative morbidity. Nonsurgical strategies comprise repetitive percutaneous fluid aspiration or percutaneous sclerotherapy. OK-432 has been used to treat congenital lymphatic malformations with several reports of promising results. We hypothesized that it is more beneficial than repetitive percutaneous fluid aspiration for the treatment of symptomatic lymphocele.

Methods: Two cohorts of melanoma patients who developed recurrent lymphocele after lymph node dissection from January 2013 to August 2017 were compared. The first cohort was treated with repetitive percutaneous fluid aspiration (n = 20). The second cohort received OK-432 sclerotherapy (n = 20). Primary end points were overall treatment duration, number of treatment sessions, and the clinical success in both cohorts. Secondary end points were surgical site infection rate, need for additional antibiotic treatment, wound healing disorders, and the need for revision surgery.

Results: Mean overall duration of treatment with sclerotherapy was significantly shorter than with repetitive aspiration (9.4 ± 7.2 vs 47.5 ± 31.9 days, $P < 0.01$). Mean number of sclerotherapy treatment sessions were 2.5 ± 1.2. Clinical success with OK-432 was 19 of 20, and that with repeated aspiration was 7 of 20 ($\chi^2 = 15.82$, $P < 0.001$). No surgical site infection occurred in the sclerotherapy cohort, which was significantly lower than those treated with repetitive aspiration ($P < 0.03$). Surgical revision was mandatory in 12 of 20 patients who were treated with repetitive aspiration, and only 1 of 20 patients in the sclerotherapy cohort.

Conclusion: Sclerotherapy with OK-432 for the treatment of postoperative lymphocele is highly beneficial with a significant reduction of morbidity and the overall treatment time compared with repetitive aspiration.

Key Words: lymphocele, sclerotherapy, lymph fistula, therapy, lymph node dissection

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A chronic fluid accumulation after lymph node dissection is derived from severed afferent lymphatic vessels at the site where tissue has been removed and is referred to as a lymphocele.[1,2] Symptomatic lymphocele formation (LF) may occur after lymphadenectomy for various malignant tumors, with a reported incidence ranging from 40% to 50%.[3] Its incidence after lymph node biopsy is less than 7%.[4] It may cause a palpable swelling with regional discomfort or pain. Consequent tension on skin sutures may hamper primary wound healing. This may lead to prolonged in-hospital stay and/or multiple outpatient visits with increasing costs. Despite improved recognition of risk factors, such as high body mass index, dead space formation after surgery and early removal or insufficient suction of drains LF remains a common problem.[5,6] Predictive factors are the amount of tissue excised, for example, level of lymph node dissection, radiation at the operating site, or systemic adjuvant chemotherapy before surgery. Muscle flaps are efficient in reducing dead space and postoperative chronic fluid accumulation primarily in selective high-risk patients and in revision surgery.[7] The use of fibrin sealants has been suggested to prevent LF, but a meta-analysis found that until now trials have been too small and methodology has been poor.[8] A combination of capsule excision and selective lymph vessel ligation with nonabsorbable sutures and titanium clips may increase the clinical success.[9,10] However, when there is a high lymphatic upload through a main pathway producing high pressure, simple ligation might come off or fail. Reconstructive lymphatic microsurgery is a new promising approach but not readily performed by all reconstructive surgeons.

Nonsurgical therapeutical strategies comprise repetitive percutaneous fluid aspiration (RA) or percutaneous sclerotherapy (ST) using different agents (eg, ethanol, polyvidone-iodine, or tetracycline). The basic mechanism of action of ST is that the lymphocele is filled with an agent, which chemically irritates the surrounding tissue and induces an inflammatory reaction. The inflammatory process leads to a fibrotic response that enables to seal the dead space, which is a reservoir for fluid accumulation. Available studies about frequently used sclerosing agents such as ethanolum absolutum, tetracycline, and povidone iodine are small scale and lack standardized procedures without proving superiority.

OK-432 (Picibanil; Chugai Pharmaceutical Co Ltd, Tokyo, Japan) was developed in 1967 by Okamoto H. initially as an anticancer agent for malignant pleural effusion (Chemical Abstract Services Number: 39325-01-4). Meanwhile, it has gained popularity among interventional radiologist owing to its sclerosing effect.[11] Pharmaceutically OK-432 is a special preparation of the low-virulent strain "Su" of a penicillin-G–treated group A *Streptococcus pyogenes* and possesses cell regulatory activity.[12–14] It leads to an elevation of many soluble cytokines, such as interferon-γ, interleukin 1 and interleukin 2, tumor necrosis factor, and activates neutrophils, macrophages, natural killer cells, and T cells.[14–16] The sclerosing effect seems to be related to its immunomodulatory activity. It was shown that OK-432 induces an inflammatory reaction, as seen in a bacterial infection and that it additionally causes regression by inducing specific apoptosis of lymphatic endothelium.[17–19] The agent has been used to treat congenital lymphatic malformations with several reports of promising results.[12,20] Some authors recommend OK-432 as the first-line therapy in the treatment of lymphatic malformations.[12,21] It has also been shown to prevent and reduce postsurgical fluid accumulation in extended latissimus dorsi flap donor sites with only minor adverse effects such as fever, erythema, paraesthesia, and swelling, which usually disappear within 4 days after intervention.[22] OK-432 has been used for the treatment of lymphoceles in the past, but studies are limited to case reports and case series.[23,24]

The purpose of this retrospective cohort study was to compare the outcome of ST with OK-432 versus RA for the treatment of

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From the [a]Department of Plastic and Hand Surgery; and [b]Department of Radiology and interventional Radiology, University Hospital Zurich, Zurich, Switzerland.

SU and GP have contributed equally to this work.

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Reprints: Nicole Lindenblatt, MD, Division of Plastic and Hand Surgery, Department of Surgery, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland. E-mail: nicole.lindenblatt@usz.ch.

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symptomatic LF after lymphadenectomy or lymph node biopsy in patients with metastatic melanoma.

MATERIALS AND METHODS

Approval to conduct this retrospective clinical study was obtained by the local institutional review board (KEK BASEC-Nb. 2016-01133) in 2016. An amendment to the protocol allowed for recruitment of cases in 2017.

Inclusion and Exclusion Criteria

For the purpose of this study, all male and female patients (>18 years old) who underwent lymph node dissection or diagnostic lymph node biopsy for metastatic melanoma with postoperative LF between January 2013 and August 2017 were included into this analysis. Lymphocele formation was treated either by RA or ST with OK-432. The latter was applied since the beginning of the study period, if 3 percutaneous fluid aspirations failed to control the refilling of the lymphocele. Patients being under immunosuppressive therapy (eg, due to solid organ transplantation), preexisting infection at the surgical site, or ongoing intravenous drug abuse were excluded from this analysis. Patients with surgical biopsies before dissection as well as patients with prior detected distant metastasis were excluded. Patients with preexisting severe skin disease such as atopic dermatitis, acne inversa, and other lymphocutaneous fistula, and concomitant treatment with antibiotics or chemotherapy were also excluded.

Patients

A systematic query of all operation reports and clinical follow-up data between January 2013 and August 2017 identified a total of 40 patients who met the inclusion criteria and had no reasons for exclusion. Thus, 18 women and 22 men (mean ± SD age, 61 ± 13 years) were included into this analysis. During the study period, the institutional treatment algorithm has changed from RA alone to ST with OK-432. Of the total cohort, 20 patients were treated with RA alone, and n = 20 patients were treated with ST. All clinical data were derived from the electronic patient files. Patient demographics including risk factors for LF are displayed in Table 1. Patients treated with ST were significantly older; otherwise, patient characteristics of both cohorts were comparable.

Surgery

Patients in both cohorts received level I/II axillary or inguinal lymph node dissection or lymph node biopsy in a standard fashion at our institution: dissection by electrocauterization was the preferred method. Lymphatic vessels that could be identified during lymph node dissection were ligated, clipped, or closed by electrocauterization according to surgeon's preference, as there is neither a standardized technique nor a scientific consensus on this issue so far. Muscle flaps to reduce dead space formation are not performed because of surgeon's preference and because there is also no scientific consensus on its benefit so far. Wound closure was performed by subcutaneous absorbable sutures combined with absorbable intracutaneous running sutures. Intraoperatively, a standard 12-gauge suction drain was placed, which was removed the latest by the 10th postoperative day to achieve wound healing. After lymph node biopsy, no suction drain was placed. After removal of the drain, patients were followed up in the outpatient clinic for wound healing.

Percutaneous Repetitive Fluid Aspiration

Twenty patients with symptomatic LF were followed up and treated according to the new institutional algorithm in intervals of 7 days. These patients were treated with RA for a maximum of 3 times. Ultrasound guidance is generally not performed at the authors' institution, and aspirated volumes were unfortunately not documented. In case of persistent lymphocele, patients were sent to the interventional radiology department for ST. In case of wound dehiscence or a surgical site infection (SSI), surgical revision including microscopic lymphatic vessel ligature or lymphovenous anastomosis was performed, if feasible.

TABLE 1. Patient Characteristics of Patients Treated With RA or ST With OK-432

	ST OK-432 (n = 20)	RA (n = 20)	*P**
Age, y†	65 ±12	56 ± 6	**0.02**
Sex‡			
Male	13	9	
Female	7	11	
BMI, kg/m^2†	26 ± 4	26 ± 6	0.91
Smoking‡	3	7	0.06
Diabetes‡	1	2	0.31
Axillary‡	9	5	0.19
Lymph node dissection	8	5	
Lymph node biopsy	1		
Inguinal‡	11	15	0.19
Lymph node dissection	9	13	
Lymph node biopsy	2	2	

Bold data indicates statistically significant.

*A P value of <0.05 is considered significant.

†Data are represented as mean ± SD and (range).

‡Data are represented as number of patients.

BMI, body mass index; Smoking, positive when actual or any smoking in the past years ≥10 pack-years.

ST With OK-432

All patients underwent ultrasound of the lymphocele before the first ST to determine the extent and volume of the lymphocele. Patients were then prepped and draped in a sterile fashion. Under sonographic guidance, an 8.5F drain (Multipurpose Drainage Catheter; Cook Medical, Bloomington, Indiana) was placed via trocar technique. Additional side holes were made before placement to ensure that the entire collection is drained sufficiently. The locking loop was formed and the catheter fixed at the skin level with sutures. A stopcock was attached to the drain. After catheter placement, the entire fluid was aspirated, and the amount of fluid was noted. OK-432 was dissolved in 1 mL of sterile distilled water and further diluted with 9 mL of saline (0.9%) in a 10-mL syringe. This was done to overcome the dead space of the catheter. The 10-mL preparation of OK-432 was then injected through the drain into the lymphocele, and the stopcock was closed. At the first ST session, patients were monitored in the interventional unit for 1 hour. Before discharge, OK-432 was completely aspirated because of patient comfort. All patients received a calibrated drain bag. Patients were asked to connect the drain with the drain bag once a day and to note the amount of fluid. Moreover, patients were informed about potential adverse effects of OK-432, which are fever not higher than 38°C, skin redness over the lymphocele, and flulike symptoms (headache, abnormal fatigue). All patients were followed up at an interval of 7 days at the interventional radiology outpatient clinic. At every follow-up visit, an ultrasound of the lymphocele was performed. Depending on the average fluid drainage per day and sonographic appearance of the lymphocele, another ST was performed. Effective ST shows a change in the sonographic appearance of the lymphocele with an increase of hyperechogenic septa that finally end up in a honeycomb-like appearance (Fig. 1). In case of complete cessation of fluid drainage, the drain

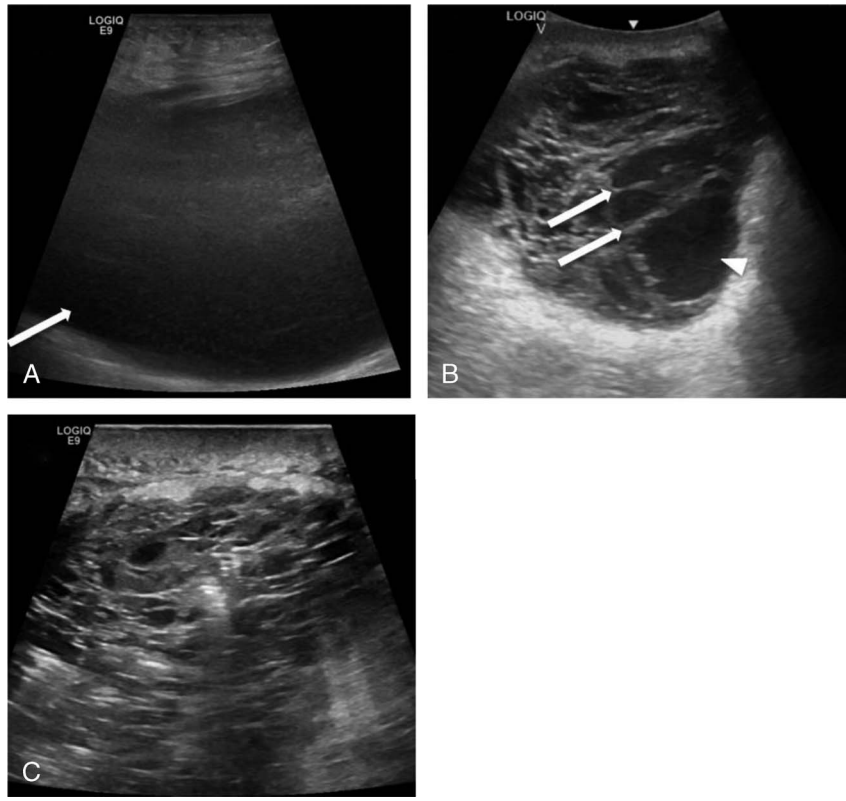

FIGURE 1. A 74-year-old man with metastatic malign melanoma and with a large symptomatic lymphocele after inguinal lymph node dissection. A, Ultrasound before the first ST shows a hypoechogenic collection (white arrow). B, Ultrasound after 2 ST with OK-432 displays multiple hyperechogenic septae (white arrow) but still some remnant collections (white arrowhead). C, After the third ST, the lymphocele has a honeycomb-like aspect. No more fluid could be drained, and the drain was removed.

was removed. The catheter entry site at the skin was left open. Procedure and doses were standardized across all patients.

OK-432 had been initially obtained for the treatment of congenital cystic lymphatic malformations by the authors' predecessors. However, because the institution is not a children's hospital, the agent was readily available to be used for the treatment of chronic postoperative lymphocele. Incidentally, shortly after the end of the study period, in October 2018, Chugai Pharmaceuticals Co Ltd officially announced that they were suspending the development of OK-432. OK-432 is no longer available.

Primary and Secondary Outcomes

Primary end points were as follows: overall treatment duration, number of treatment sessions, and the clinical success in both cohorts. Clinical success is defined as no recurrence of the lymphocele or complete cessation of fluid production measured by the drain. Overall duration of treatment started after a total of 3 percutaneous aspirations.

Secondary end points were as follows: SSI rate, need for additional antibiotic treatment, wound healing disorders, and the need for revision surgery. In the subgroup that received ST with OK 432, adverse side effects were analyzed. Moreover, development of lymphedema was noted.

Statistical Analysis

Statistical analysis was performed by using commercially available software (IBM, SPSS statistics, Version 23; SPSS Inc, Chicago, Illinois). Continuous variables are expressed as mean ± SD. Categorical variables are expressed as frequencies or percentages. Results were tested for normality using the Kolmogorov-Smirnov test. Normal distributed variables were compared by using the paired-samples *t* test. A *P* value of less than 0.05 was considered statistically significant. This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

RESULTS

Forty patients with recurrent LF after lymph node dissection for melanoma treatment were included in this study. Twenty patients with RA of lymphocele were assigned to the first cohort. The second cohort consisted of 20 patients who underwent ST with OK-432 after 3 aspirations failed to control the lymphocele. Patients who received ST were significantly older; otherwise, patient characteristics of both cohorts were comparable. Distribution of axillary and inguinal lymph node dissections did not significantly differ in both cohorts (Table 1).

Primary End points

Overall, the mean treatment duration was significantly shorter in the ST cohort than in the group that received RA only (9.4 ±1.2 vs 47.5 ± 31.9 days, $P < 0.01$; Fig. 2). As stated previously, duration of treatment was counted after 3 RAs in each cohort. In the ST cohort, the mean number of treatment sessions was 2.5 ± 1.2, which was significantly less than that in the RA cohort (4.1 ± 1.8, $P < 0.01$). The mean number of ST sessions of axillary (2 ± 1 sessions) and inguinal lymphoceles (3 ± 2 session) did not significantly differ ($P > 0.2$). Clinical successes were n = 7/20 patients for RA and n = 19/20 patients for ST.

Secondary End Points

Surgical site infections were seen in 5 of 20 patients treated with RA, whereas none of the patients who were treated with OK-432

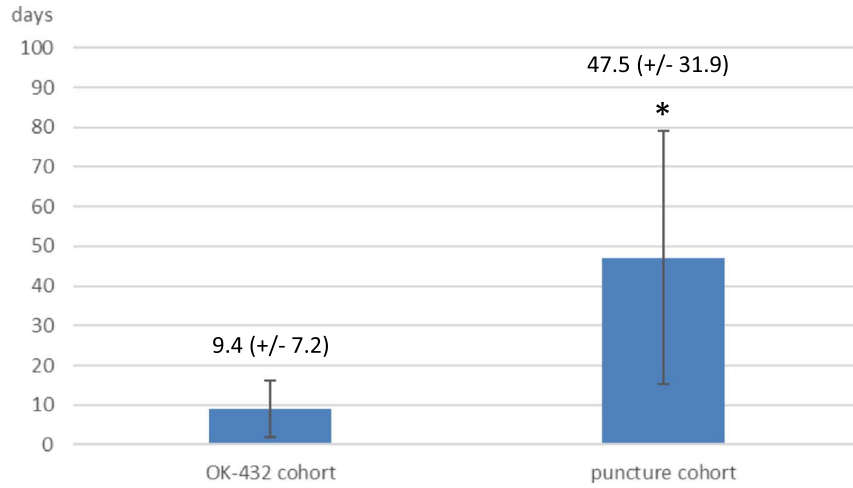

FIGURE 2. Comparison of mean duration of treatment (number of days after 3 RAs in both groups). *$P < 0.05$. full color online

developed SSI ($P < 0.03$; Fig. 3). Antibiotic therapy was mandatory in 5 patients in the RA cohort. No additional antibiotic therapy had to be installed in the ST cohort. Wound healing disorders were seen in 13 of 20 patients treated with RA and in 1 of 20 patient who underwent ST. Patients treated with ST had a significantly lower rate of revision surgeries than did patients treated with RA ($P < 0.01$). Revision surgery of 1 patient in the ST cohort was due to late wound dehiscence caused by skin necrosis after epidermolysis, which was present already immediately after the operation. Reasons for the high percentage of revision surgeries in the RA cohort were infectious wound breakdown. In the ST cohort, 5 patients had OK-432–related adverse effects (mild fever, n = 2; localized erythema and swelling, n = 3). All of these adverse effects were temporary and resolved within 2 to 3 days without taking any further actions. None of these patients presented to the emergency unit or had to be hospitalized because of these effects. One patient underwent percutaneous aspiration 8 times during a period of 3 months and developed lymphedema during the duration of treatment with RA. No patient developed lymphedema over the course of ST with OK-432.

DISCUSSION

Recurrent lymphocele after lymph node dissection or biopsy for diagnostic and therapeutic reasons remains a frequent clinical problem. Symptomatic LF can be expected in every second patient after lymphadenectomy.[3] Postoperative treatment options are limited, and repeated percutaneous aspiration is often the treatment of choice. However, RA increases the risk of local infections and other complications that may delay patient recovery and markedly add to patient discomfort. Given the incidence and consequences of symptomatic lymphocele, there is a demand for an effective method to treat LF.

Results of this retrospective, comparative cohort study demonstrate that ST using OK-432 significantly shortens the overall treatment time with a significantly lower amount of outpatient visits compared with traditional repetitive fluid aspiration. Moreover, ST with OK-432 allows for a further reduction in morbidity associated with LF. Surgical site infections were not seen in patients treated with ST, which is probably related to the catheter that allowed for intermittent draining of lymphocele cavity. The presence of a drain further decreases skin closure tension, which allows for primary wound healing. One major advantage is that the rate of revision surgery was significantly decreased using ST. In 19 of 20 patients who received ST with OK-432, treatment was successful and no further therapy was necessary. Results presented in this study show a significant effect of ST with OK-432 on frequency and overall duration of treatment. Ethanolum absolutum, for example, is an inexpensive and readily available sclerosing agent. Because its application can be painful, it sometimes has to be instilled at least under moderate sedation. Only a few small-scale studies imply that weekly instillations of ethanol are necessary to achieve complete resolution within 1 month.[25,26] In a previous study, povidone iodine solution was instilled 2 to 3 times daily through a catheter into the cavity, increasing risk of infection.[26] Symptoms of iodine toxicity might occur and serum iodine

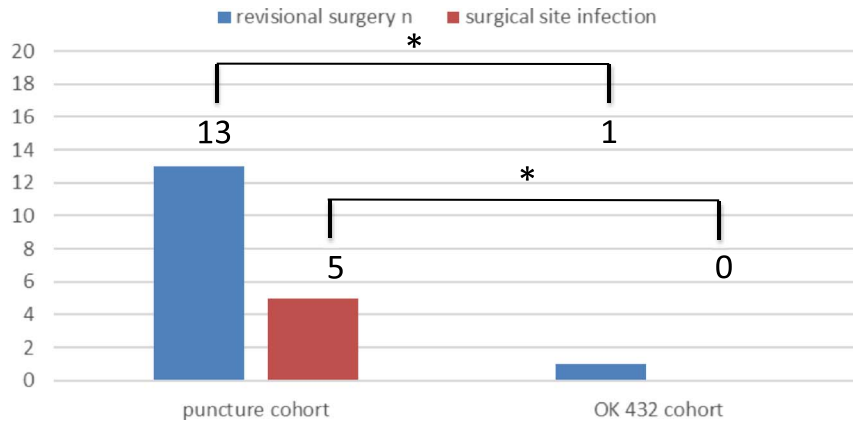

FIGURE 3. Number of SSI and revision surgeries in both groups. *$P < 0.05$. full color online

levels need to be monitored, as lethality has been reported after continuous mediastinal irrigation with povidone iodine.[27] Lesions healed within 4 to 8 weeks after weekly application of tetracyclines, whereas reported complications included severe burn sensation, reduced skin mobility or tightness, and contour deformity.[28] Preventive use of tetracyclines may even increase the risk of chronic fluid accumulation.[29] In addition, tetracycline and polyvidone-iodine cannot be used in patients with allergies to certain antibiotics or iodine. A cost analysis and patient satisfaction survey was not included in this study. However, based on the results of this study, we hypothesize that OK-432 most likely reduces costs and patient discomfort as it decreases the number of revision surgeries and shortens overall treatment time compared with RA. Studies comparing different sclerotherapeutic agents in specific have to be conducted to demonstrate significant supremacy of one agent over the other.

Regarding postinjection complications, OK-432 adverse effects were minor and limited to mild fever and local erythema and swelling in our patient collective. We did not conduct laboratory test, but none of our patients presented emergently or had to be hospitalized because of adverse effects of the treatment. We did not use OK-432 in immunocompromised patients because the course of adverse effects of OK-432 in immunocompromised patients is unknown and expected to be more intense. Also, ST with OK-432 requires tissue adhesion, which is very limited in an immunocompromised patient. In the literature, several OK-432 injection adverse effects were reported in patients mainly treated for lymphatic malformations. Erythema, discomfort, induration, swelling at the injection site, and fever that resolved with paracetamol and nonsteroidal anti-inflammatory drugs after 1 to 3 days are the most often reported ones.[30–32] In patients with head and neck lymphatic malformations, elevated serum levels of IP-10, C-reactive protein, and leukocyte indicated that OK-432 ST induces systemic immune responses in patients with LM.[31] However, all 17 patients in this study experienced only local tenderness, and most of them had fever related to OK-432 ST. Only one patient developed a peritonsillar abscess at 16 days after the second OK-432 injection into his macrocystic lesion in the floor of the mouth and submandibular space.[31] Another study about the treatment of head and neck lymphangiomas in 15 children reported postinjection anemia that resolved only after concentrated red blood cell transfusion in one child and only transitory increase of platelets' concentration, with spontaneous resolution within 1 month in 6 other.[32] No electrolyte alteration was recorded in that study. We hypothesize that its use for lymphatic malformations is more invasive.

There is also a potential risk of developing postinterventional lymphedema, as OK-432 leads to specific apoptosis of lymph endothelium and because of the localized inflammation to an adhesion of the wound bed. We only followed up our patients until the lymphocele was resolved. During that period, we did not see any lymphedema in the ST cohort. One patient in the RA cohort developed lymphedema. Lymphocele formation itself is a risk of developing lymphedema.[33] Conclusively, further prospective wide-scale clinical studies and long-term follow-ups are needed to clarify and prove its safe application for recurrent lymphocele. In general, we strongly advise to inform patients about the risk of recurrent lymphocele and to educate all patients who develop symptomatic lymphocele as to the anticipated course of risks and treatment.

Based on our clinical experience, we developed an algorithm for our clinic on how to approach recurrent lymphocele (Fig. 4). This algorithm seemed to be useful and practical, although, among its several components, effectiveness has to be proven yet.

If LF is present and wound healing is not compromised, we aspirate the lymphocele a maximum of 3 times and refer the immunocompetent patient to ST with OK-432 if lymphocele is persistent. If wound healing is compromised, the fistula is apparent, or an immunocompromised patient already received 3 percutaneous aspirations, we perform revision surgery. Depending on wound bed condition, we combine debridement with secondary wound closure or prepare the wound bed with negative pressure therapy. Lymphatic microsurgery is another emerging treatment of option for reconstructive surgeons. It was shown that inguinal lymphocele prevention was possible by primarily indocyanine green mapping of wound bed area.[34] Refractory groin lymphocele was treated successfully by surrounding supermicrosurgical lymphaticovenous anastomosis.[35,36] Before wound closure, we routinely use indocyanine green to detect lymphatics, and if suitable, we conduct lymphovenous or lympholymphatic anastomosis. We ligate and clip lymphatics that are not suitable for microsurgical reconstruction. If necessary, we perform musculocutaneous or muscle flaps to

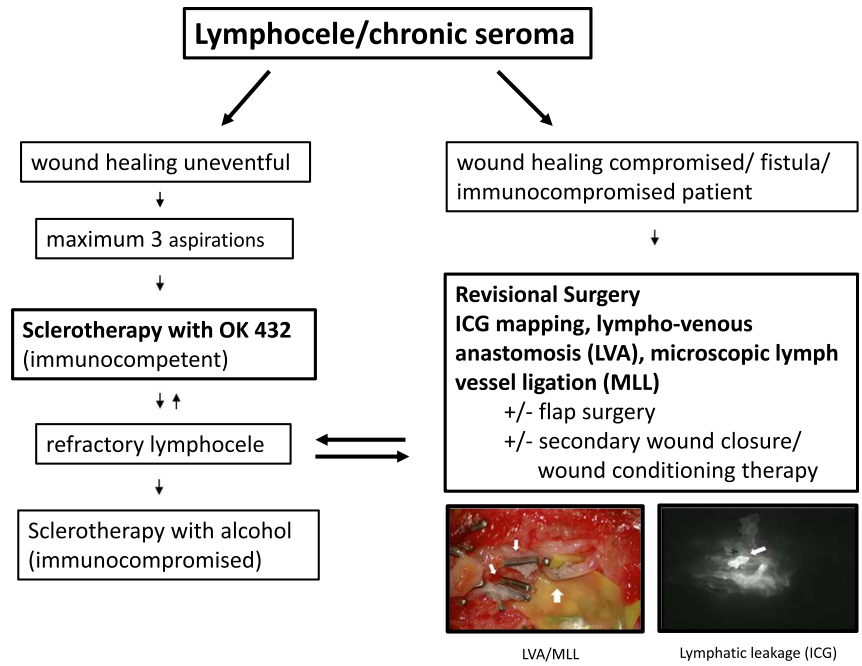

FIGURE 4. Algorithm on how to approach chronic postoperative lymphocele. full color online

close the dead space or skin defect. If lymphocele persists after ST, we perform revision surgery. If lymphocele still persists after revision surgery and the patient is immunocompetent, we perform ST with OK-432. In immunocompromised patients, alcohol may be used because OK-432 will not cause an immune response and therefore will not be effective.

Limitations

Several limitations apply to this study. First, the study is of a retrospective nature and long-term follow-up data are not available to this study. The number of patients in both cohorts is limited and groups are heterogeneous, as lymph node dissections and diagnostic lymph node biopsies are very different surgeries, although most patients underwent lymph node dissections. Furthermore, the impact of differences in tumor stage has not been analyzed and included into this study. Because of the lack of documentation, aspirated volumes and lymphocele sizes could not be compared. In fact, the volume aspirated in each clinical encounter and the trend of decreasing volume will provide valuable data and meaningful comparison. The effectiveness as well as complication rate and adverse effects have to be tested and compared in larger randomized patient cohorts and prospectively to further prove the efficacy of OK-432.

CONCLUSION

Compared with RA, ST with OK-432 of symptomatic lymphoceles after lymph node dissection shows a high clinical success with a significant reduction of the overall treatment time and number of outpatients visit. Moreover, ST allows for a significant reduction in SSIs and revision surgeries.

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